IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: **Yuan-Di C. Halvorsen et al.**

Serial No.: **Continuation of 09/554,868** Art Unit: **1655**

Filed: Examiner: Chakrabarti

For: **DIFFERENTIATION OF ADIPOSE STROMAL CELLS INTO OSTEOBLASTS AND USES THEREOF**

Assistant Commissioner for Patents
Box IDS
Washington, DC 20231

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL

Sir:

Pursuant to the duty of disclosure under 37 CFR §§ 1.56, 1.97 and 1.98, Applicants cite the publications listed on the accompanying PTO-1449. Copies of all listed references are enclosed. The assignee of the present application, Artecel Sciences, Inc. has obtained a nonexclusive license to the technology described in PCT Publication No. WO 00/53795 (PCT/US00/06232, filed March 10, 2000), published on September 14, 2000 and related applications, including the U.S. patent application claiming priority to Serial Nos. 60/123,711 filed March 10,1999, and 60/162,462 filed October 29, 1999 from the University of Pittsburgh.

Applicants bring to the Examiner's attention the following U.S. applications which are co-pending within the United States Patent and Trademark Office:

Serial No.	Inventor	Filed	Title
09/573,989	Gimble et al.	May 17, 2000,	Use of Adipose Tissue-Derived Stromal Cells for
09/638,544	Gimble et al.	August 24, 2000	"Multiple Mesodermal Lineage Differentiation
09/793,173	Gimble et al.	February 26, 2001	Adipose Tissue-Derived Stromal Cells and Uses Thereof"
09/585,821	Halvorsen et al.	June 1, 2000	"Methods and Compositions for the Differentiation of Human Preadipocytes Into Adipocytes"

09/592,019	Mousse et al.	June 12, 2000	"Modulation of the Sulfonylurea Receptor and Calcium in Adipocytes for Treatment of Obesity/Diabetes"
09/592,421	Mousse et al.	June 12, 2000	"Modulation of the Sulfonylurea Receptor and Calcium in Adipocytes for Treatment of Obesity/Diabetes"

Relevant Art Cited By the Examiner in the Parent Application

During the prosecution of the parent application, US 09/554,868, the Examiner cited the following references as potentially relevant: US Patent Nos. 5,446,143 to Simpson et al, 5,786,207 to Katz et al., 5,226,914 to Caplan et al, and Poliard et al. (J. Cell Biol (1995), 130(6): 1461-1472). A copy of the first Office Action in the parent case is included for the Examiner's reference. Applicants would like the Examiner to consider the following remarks concerning these documents, with reference to the presented claims.

US Patent No. 5,446,143

The '143 patent to Simpson et al discloses the identification and use of two unique 5'-untranslated exons of the CYP19 gene which code for the microsomal enzyme, aromatase cytochrome P450. This enzyme is important in estrogen biosynthesis. The invention in the '143 patent is the identification of these exons in adipose tissue and adipose stromal cells under certain specific culture conditions (column 2, line 57 through column 3, line 16). A further aspect of the '143 invention is that certain hormones such as dexamethasone or glucocorticoids stimulate stromal cells to produce these products (column 3, lines 5-16; column 7, lines 12-19). However, Simpson et al do not disclose an adipose tissue-derived stromal cell that can be differentiated into a cell with non-adipocyte cell lineage properties.

US Patent No. 5,786,207

During the prosecution of the parent application, the Examiner alleged that the '207 patent inherently teaches an adherent isolated adipose tissue-derived stromal cell that exhibits at least one characteristic of a non-adipocyte cell lineage (column 2, lines 19-35). It was argued that this reference inherently teaches an isolated adipose tissue-derived stromal cell in combination with a substance that promotes differentiation. Applicants disagree.

The statements in the '207 patent at column 2, lines 19-35 teach that adipose tissue is a source of several different cell types including adipocyte, adipose precursor cells, fibroblasts and vascular endothelial cells (lines 19-23). Further, Katz states that adipose precursor cells can be isolated from adipose tissue and differentiated into adipocytes through chemical manipulation (lines 26-32). In addition, the '207 patent points out that it is also known that it is possible to dedifferentiate mature adipocytes and re-differentiate them into fat cells (lines 33-35). Katz makes the following comments in the Background of the Invention: "Further, adipose tissue is a potential source of extracellular matrix components, bioactive growth factors, paracrine and endocrine hormones, and perhaps even the progeny of mesenchymal stem cells at a development stage which still confers multipotent plasticity (column 2, lines 22-26)." Therefore, Katz affirmatively admitted that he had no idea at the time whether adipose tissue contains any cells that are capable of differentiation into other cell types, much less how to isolate those cells or how to accomplish the differentiation.

This complete lack of knowledge was further confirmed by Katz when he and others filed for the first time a patent application announcing that they had identified adipose-derived cells capable of differentiation into other cells on March 10, 1999 (U.S.S.N. 06/123,711; PCT

WO 00/53795)), almost two years after the filing of the application leading to the '207 patent. However, the present application, first filed on December 2, 1997, was the first to demonstrate an isolated human adipose-tissue derived stromal cell that exhibits at least one characteristic of a non-adipocytic cell lineage.

The earlier filed '207 patent is characterized by Katz in the later filed WO 00/53795 as merely disclosing an alternative **device** to facilitate the isolation of fat cells (page 4, lines 43-46).

Poliard et al

During the prosecution of the parent application, the Examiner pointed to the Poliard reference which teaches that ascorbic acid or beta-glycerophosphate can promote differentiation in competent C1 cells.

Applicants draw the Examiner's attention to the fact that C1 cells are derived from **mouse embryonic tumors**, specifically, teratocarcinomas and are classified as embryonal carcinoma -derived cells. Embryonal carcinomas are highly malignant germ cell tumors arising from germ cell differentiation. The C1 cell line is immortal in cell culture and like other germ cell tumor cell lines, has the potential for differentiation along various cell lineages. Most importantly, these cells are **NOT** adipose-derived. Furthermore, one skilled in the art would not have any rational scientific basis for concluding that a non-immortalized adult-**adipose-derived** cell would behave in culture the same as an embryonic tumor-derived cell line.

It was suggested by the Examiner in the first Office Action of the parent application that "Figure 9 of the Poliard reference teaches that ascorbic acid or beta-glycerophosphate promotes differentiation in competent C1 stem cells which have all the properties of adipose stromal

cells." This is incorrect. As stated in the reference on page 1470, second column, third paragraph, "Figure 9 summarizes [the] current views about the developmental stages of the C1 mesodermal **cell line**." The Poliard reference merely describes that the immortalized **mouse embryonic tumors** can develop into mature adipocytes. The reference never teaches or suggests that stromal cells can be found in adipose tissue, how to isolate them or how to differentiate them. In fact, the Poliard reference states that only "[i]n sparse cultures, [does the mouse embryonic cell line] exhibit the properties of a true progenitor cell." On page 1470, column 1, third paragraph to column 2, second paragraph, Poliard hypothesizes that C1 cells resemble preadipocyte cell lines. The article never suggested that preadipocytes could be differentiated into a cell that exhibits a characteristic of a non-adipocyte. One skilled in the art would not confuse immortalized teratogenic cell lines with isolated adipose-derived cells. In addition, although the reference states "Under AA and beta-GP culture conditions, C1 cells appear unequivocally committed towards the osteogenic pathway (page 1462, column 1, last sentence), one skilled in the art would not assume this to be true for other types of cells.

US Patent No. 5,226,914

The '914 patent teaches the isolation and purification of **bone marrow-derived** progenitor cells and their ***in-vivo*** differentiation into bone cells within ceramic grafts. Applicants' invention is an adipose-derived stromal cell that has been induced *in vitro* to express at least one characteristic of a non-adipocyte cell. The '914 patent does not teach or even suggest an adipose-derived cell. Furthermore, one skilled in the art of adipose cell differentiation would not look to the '914 patent for guidance since adipose-derived cells are phenotypically and

genotypically different from bone marrow cells. Isolating and differentiating cells from one source, does not guarantee the presence of, much less, success in isolating and differentiating, cells from other sources.

U.S. Patent No. 6,200,606 and PCT WO/0053795

The Examiner's attention is further directed to two references that have been cited in the accompanying IDS. U.S. Patent No. 6,200,606 to Peterson et al. describes the use of cartilage or bone precursor cells from hematopoietic and non-hematopoietic cells and their use in bone and cartilage repair. The precursor cells are used for *in vivo* bone or cartilage repair by transplanting the cells, with or without a carrier material and without the need for *in vitro* culturing of the cells, to sites in the body requiring bone or cartilage repair. The method involves implanting CD34+ cells that are isolated from peripheral blood, marrow or adipose tissue, and then allowing the cells to form into bone or cartilage cells in an *in vivo* environment. The patent states that

> While the factors that determine biological differentiation are not fully understood, it is known that precursor cells will differentiate into bone or cartilage if transplanted to a site in the body needing repair. Precursor cells isolated by the present method can be implanted alone or premixed with bioactive compounds, for example, cell signaling molecules, including growth factors.

'606 patent, column 10, lines 62-69 and column 11, line 1. Thus the patentees admit that they do not understand what is required to induce differentiation of these cells but teach that it can occur *in vivo*. There is no teaching of differentiating human adipose-derived stromal cells *ex vivo* or

producing *ex vivo* an isolated human adipose tissue-derived stromal cell that exhibits at least one characteristic of a non-adipocyte cell lineage. Example 6 of the '606 patent describes the isolation of microvascular cells from rat epididymal fat pads. Example 7 of the '606 patent describes the *in vitro* differentiation of rat epididymal fat pads.

PCT WO/0053795 describes adipose-derived stem cells and lattices. The assignee of the present invention, Artecel Sciences, Inc. holds a non-exclusive license interest in this and related applications, including the pending U.S. equivalent of the PCT application. Applicants enclose a copy of PCT WO/0053795 as well as its priority documents. PCT WO/0053795 is not currently prior art against the pending claims because it was published on September 14, 2000, and the present case was filed on May 19, 2000.

If the Examiner determines any additional fee is required, the Commissioner is authorized to charge such fees associated with this paper to Deposit Account No. 11-0980.

Respectfully submitted,

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				First Named Inventor	**Halvorsen**
				Group Art Unit	1655
Sheet	1	of	5	Attorney Docket Number	ART 1030 CON (08140.105014)

jc828 U.S. PTO 10/061214 01/30/02

U.S. PATENT DOCUMENTS

Examiner Initials *	Cite No. [1]	U.S. Patent Document Number (if known)	Kind Code	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pgs, Clmns, Lns, Where Relevant Passages/Relevant Figs Appear
	AA	5,486,359		Caplan *et al*	01/23/1996	
	AB	5,786,207		Katz *et al.*	07/28/1998	
	AC	6,153,432		Halvorsen *et al.*	11/28/2000	
	AD	6,200,606	B1	Peterson *et al.*	03/13/2001	
	AE	60/123,711		Katz *et al.*	03/10/1999 (filed)	
	AF	60/163,462		Katz *et al.*	10/29/1999 (filed)	

FOREIGN PATENT DOCUMENTS

Examiner Initials *	Cite No. [1]	Foreign Patent Document Office [3]	Number	Kind Code [2] (if known)	Date of Publication of Cited Document DD-MM-YYYY	Country	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T [6]
	AG	WO	99/28444	A1	10/06/1999	PCT		
	AH	WO	00/53795	A1	14/09/2000	PCT		
	AI	WO	01/62901	A1	30/08/2001	PCT		
	AK	WO	00/44882	A2	03/08/2000	PCT		

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Filing Date	
				First Named Inventor	**Halvorsen**
				Group Art Unit	1655
Sheet	2	of	5	Attorney Docket Number	ART 1030 CON (08140.105014)

OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS			
Examiner Initials *	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	BA	ASHTON *et al.*, "Formation of Bone and Cartilage by Marrow Stromal Cells in Diffusion Chambers *in Vivo*," Clin Orthop, (1980), Vol. 151, pp. 294-307.	
	BB	BECKER *et al.*, "Use of Recombinant Adenovirus of Metabolic Engineering of Mammalian Cells," Meth Cell Biol, (1994), Vol. 43, pp. 161-189.	
	BC	BENAYAHU *et al.*, "Subpopulations of Marrow Stromal Cells Share a Variety of Osteoblastics Markers," Calcif Tiss Int., (1991), Vol. 49, pp. 202-207.	
	BD	BENNETT *et al.*, "Adipocytic Cells cultured from Marrow Have Osteogenic Potential," J Cell Sci, (1991), Vol. 99, pp. 131-136.	
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	BJ	COOK *et al.*, "Osteogenic Protein-1," Clin Orthop, (1996), Vol. 324, pp. 29-38.	
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	CA	GIMBLE *et al.*, "Adipogenesis in a Murine Bone Marrow Stromal Cell Line Capable of Supporting β Lineage Lymphocyte Growth and Proliferation: Biochemical and Molecular Characterization," Eur J Immunol, (1990), Vol. 20, pp. 379-387.	
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	CC	GUNDLE *et al.*, "Human Bone Tissue Formation in Diffusion Chamber Culture In Vivo by Bone-Derived Cells and Marrow Stromal Fibroblastic Cells," Bone, (1995), Vol. 16, pp. 597-601.	
	CD	HAUNER *et al.*, "Promoting Effect of Glucocorticoids on the Differentiation of Human Adipocyte Precursor Cells Cultured in a Chemically Defined Medium," J Clin Invest, (1989), Vol. 84, pp. 1663-1670.	
	CE	HAYNESWORTH *et al.*, "Characterization of Cells with Osteogenic Potential from Human Marrow," Bone, (1992), Vol. 13, pp. 81-88.	
	CF	HERRON *et al.*, "The Failure of Ethylene Oxide Gas-Sterilized Freeze-Dried Bone Graft for Thoracic and Lumbar Spinal Fusion," Spine, (1989), Vol. 14, pp. 496-500.	
	CG	KABAN *et al.*, "Treatment of Jaw Defects with Demineralized Bone Implants," J Oral Maxillofac Surg, (1982), Vol. 40, pp. 623-626.	
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	CI	KAPLAN *et al.*, "Clinical Vignette Fibrodysplasia Ossificans Progressiva (FOP)," J Bone Min Res, (1997), Vol. 12, p. 855.	
	CJ	KATZER, "Histopathology of Rare Chondroosteoblastic Metaplasia in Benign Lipomas," Path Res Proct, (1989), Vol. 184, pp. 437-443.	
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	DB	LANE, "Current Approaches to Experimental Bone Grafting," Ortho Clin N Amer, (1987), Vol. 18, pp. 213-225.	
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	DE	MULLIKEN *et al.*, "Use of Demineralized Allogeneic Bone Implants for the Correction of Maxillocraniofacial Deformities," Ann Surg, (1981), Vol. 194, pp. 366-372.	
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	DL	SUMMERS *et al.*, "Donor Site Pain from the Ilium," J Bone Joint Surg, (1989), Vol. 71B, pp. 677-680.	

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	EB	TURNER *et al.*, "Patient Outcomes after Lumbar Spinal Fusions," JAMA, (1992), Vol. 268, pp. 907-911.	
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